

## CENTRAL FAX CENTER

APR 24 2006

**DECLARATION OF ANDREAS KOECKOWSKI**

REAS KERBROSKI  
Social No. 4B/PEA 688

• 10/070,093

NEKT 0019  
E-1-13

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In re Application of:  
Peter York, et al.**  
**Serial No.: 10/070,093**  
**Confirmation No.: 7330**  
**Filed: July 31, 2002**  
**For: Co-formulation Methods  
and Their Products**

Group Art Unit: 1615

Examiner: Eric E. Silverman

MAIL STOP AF  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

**CERTIFICATE OF FACSIMILE TRANSMISSION UNDER  
37 CFR 1.8**

I hereby certify that this correspondence and the documents referred to as attached thereto are being facsimile transmitted to the U.S. Patent and Trademark Office to the fax number indicated by the Examiner, namely, fax number 571-273-8300 to the attention of the named Examiner, on the date below.

**DECLARATION UNDER 37 C.F.R. 51.132**

I hereby declare and state as follows:

1. That I, Andreas Kordikowski, am the Head of Technology Development of Nektar Therapeutics UK. Ltd. I have over 15 years of experience in the field of supercritical fluids (SCFs) and high pressure multi-component phase equilibria. My responsibilities include developing SCF technology for the production of active pharmaceutical ingredients (APIs) and

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providing scientific support in elucidating processing problems via the application of phase equilibria.

2. That I have a Dipl. Chem. (similar to MSc) in chemistry from the Ruhr-Universität Bochum and a Ph.D. in Physical Chemistry from the Ruhr-Universität Bochum with a focus on High Pressure Fluid Phase Equilibria.
3. That I am not one of the inventors of United States Patent Application Serial No. 10/070,093, July 31, 2002, but have read the application (herein '093).
4. That I have read the specification of the International Application published under the Patent Cooperation Treaty as International Publication No. WO 95/01221, filed June 30, 1994 (herein '221).
5. That, as a person skilled in the field of supercritical fluid technology for the production of active pharmaceutical ingredients, it is my opinion that the salmeterol xinafoate made by the method of '221 is not present in the particles in a high amorphous to crystalline form ratio. The DCS/XRD data depicted in the specification of '221 indicate Salmeterol Xinafoate with a high degree of crystallinity, most likely more than 95 %. Although the absolute amount of crystallinity cannot be determined from the XRPD diffractogram alone it can be seen that the absence of an amorphous halo, or background is proof for the high crystallinity of the Salmeterol Xinafoate. To elucidate further the difference between amorphous and crystalline samples measured by XRPD two figures are attached. The first shows a pure compound in both its crystalline and amorphous states. As can be seen from the diffractogram, the crystalline form exhibits various reflections (peaks) at different angles (2 theta) which indicate the reflection of the incident radiation at molecules in a fixed position in the crystal

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lattice. However, the amorphous form does not show any reflections as the crystal lattice is no longer present, only random noise (amorphous halo) is obtained at all reflection angles. The second figure shows a compound co-formulated with a polymer in various stages from highly crystalline to totally amorphous. In the transition from crystalline to amorphous a broadening and disappearing of the crystalline reflections can be discerned until only an amorphous halo remains.

6. That, as a person skilled in the field of supercritical fluid technology for the production of active pharmaceutical ingredients, it is my opinion that Salmeterol Xinafoate is insoluble in super critical carbon dioxide. Estimates for its solubility (as mole fraction) are lower than  $x_{(sx)} = 1 \cdot 10^{-9}$  in pure carbon dioxide at 40 °C and 200 bar.
7. That all statements made herein of my own knowledge are true and that these statements made on information and belief are believed to be true and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent resulting there from.

03 April 2006  
Date

  
Signature,  
Andreas Kordikowski

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Appendix

APPENDIX

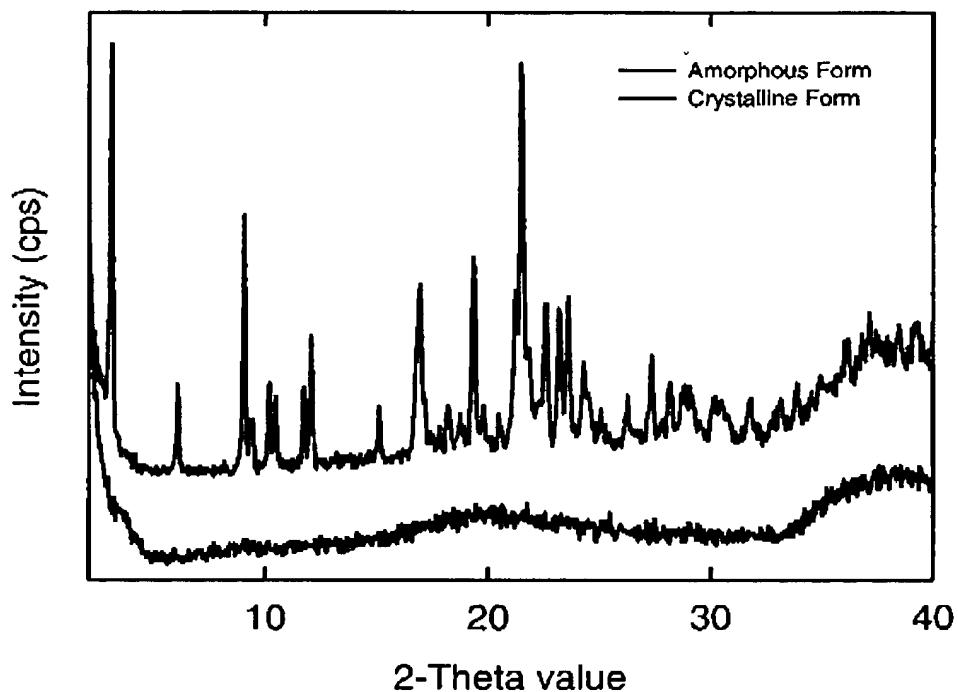


Figure 1

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Appendix

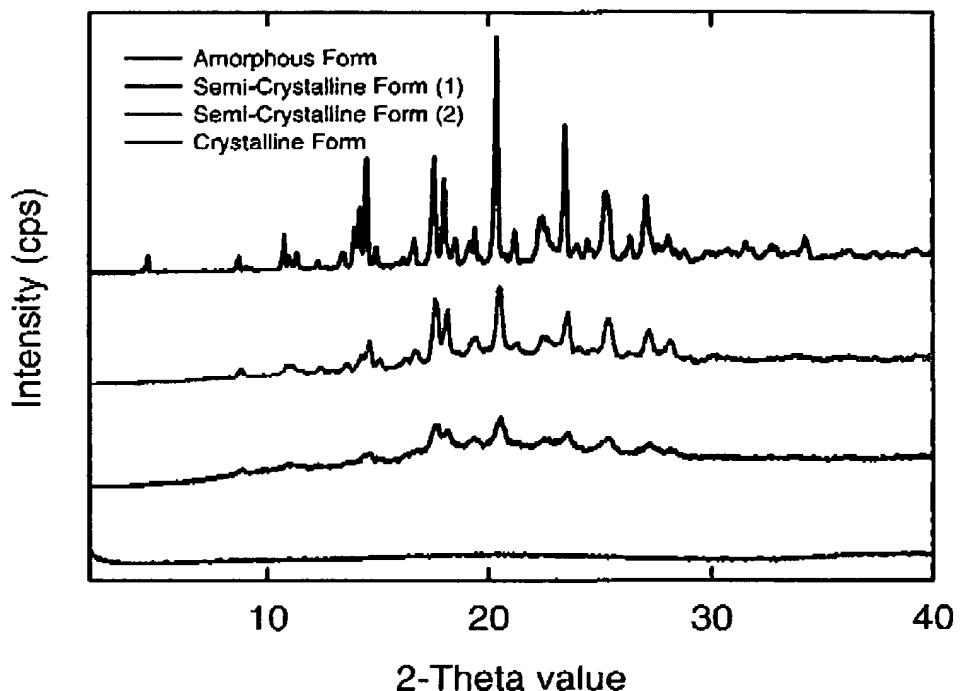


Figure 2